REMARKS

This document is in response to the Examiner's communication dated November 19, 2007 (the Office Action) and the Notice of Non-Compliant Amendment dated July 25, 2008 (the Notice). This document is also a summary of the telephone interviews conducted between the Examiner Tongue and Dr. Fahrni on July 29, 2008 and July 31, 2008.

Claims 1-22 are pending. By this Amendment, claim 2 is cancelled, claims 1, 3, 4, and 12 are amended. Claim 1 is amended to delete certain embodiments of the application. The original limitation from claim 2 is amended into claim 1. Claim 3 is amended to delete certain embodiments of the application. Dependent claims 4 and 12 are amended in view of the amendment in claim 1. Claim 12 is further amended in accordance with the agreement reached between Dr. Fahrni and Examiner Tongue.

Interview between Examiner Tongue and Dr. Fahrni

Dr. Fahrni requested an interview with Examiner Tongue to discuss how to appropriately respond to the Notice. During the interview, Dr. Fahrni inquired about the possibility of keeping claim 12 for future examination. Examiner Tongue requested the Applicants to amend claim 12 to be commensurate in scope with independent claim 1 so it could be examined together with the other elected claims. Claim 12 has been amended accordingly. The Applicants thank Examiner Tongue for allowing amended claim 12 to be included for future examination.

Restriction Requirement

Claims 1, 2, 4, 6, 7, and 10-12 are elected. Claims 3, 5, 8, 9, and 13-22 are withdrawn from further consideration as being drawn to non-elected inventions. Applicants maintain that claim 1 is a linking claim for claims 5-12 and 20-22, such that rejoinder of non-elected claims 5, 9, and 20-22 is requested upon such time as claim 1 is allowed. Elections are made for procedural purposes and no admissions are made with respect to patentability or claims construction. Additionally, the Applicants maintain the traversal of the Restriction Requirement to preserve the right of petition.

Information Disclosure Statement

An information disclosure statement is submitted with this reply. As outlined in the section below relating to 35 USC § 102, Braun et al. (2004) is submitted as evidence that only a limited number of *Moraxella catarrhalis* strains has LOS with oligosaccharides showing cross-reactivity with *Neisseria meningitidis* and human blood group antigens.

35 U.S.C. §112

I. The Examiner rejected claims 1, 2, 4, 6, 7, 10, and 11 under 35 U.S.C. §112, first paragraph that the application does not sufficiently enable people with ordinary skill in the art to use the invention. Applicants assume the Examiner intended to reject claims 1, 2, 4, 6, 7, and 10-12. Applicants respectfully disagree with this rejection.

It is well-settled that a therapeutic method need not be ready for clinical application in order to be enabled. See In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." In general, the references cited by the Examiner are directed to a different therapeutic problem and are not applicable, as explained below. Further, the amended claims are drawn much more narrowly and are believed to address the Examiner's concerns. This rejection is traversed, however, on the grounds that there is no prima facie case of nonenablement.

Breadth of the Claims

The Examiner states that the claims are broadly drawn. The claims, however, are directed specifically to the treatment or prevention of diseases due to infection by *Neisseria meningitidis*. As outlined on page 1, lines 16 to 20 of the application, there are only two forms of meningococcal disease, which are meningitis and septicaemia. The therapeutical indication in claim 1 is directed to specific and highly related conditions so that it is believed to be drawn narrowly and not broadly.

Additionally, the medicament of claim 1 comprises purified lipooligosaccharides from commensal *Moraxella catarrhalis*, the oligosaccharide portion of which being cross-reactive to

Neisseria meningitidis of serogroup B and cross-reactive to human blood group antigens. The selection of oligosaccharides of LOS with the concrete cross-reactivity renders claim 1 very specific, because only some *Moraxella catarrhalis* strains have LOS oligosaccharides which are cross-reactive with *Neisseria meningitidis* and human blood group antigens. The amended claims have been specifically drawn to only serogroup B to thereby eliminate about 12 antigens and further reduced to claim lipooligosaccharides and therefore are believed to address concerns about undue breadth.

Directions or Guidance Presented in the Specification

The Applicants discovered that LOS from *Moraxella catarrhalis*, more specifically the oligosaccharides of the LOS, are cross-reactive antigens to *Neisseria meningitides* and human blood group antigens and can be useful as a medicament for the treatment or prevention of infection by *Neisseria meningitides*.

The application provides sufficient information to people with ordinary skill in the art on how to obtain these LOS from *Moraxella catarrhalis*. On page 22, lines 21 to 31 of the application, a method for the extraction of the LOS is disclosed. As noted by the Examiner on page 7 of the Office Action, the application provides working examples from pages 51 to 55, showing how to determine cross-reactivity between *Moraxella catarrhalis*, *Neisseria meningitides* and human blood group antigens. People with ordinary skill in the art in view of the application could obtain *Moraxella catarrhalis* LOS with the required cross-reactivity by obtaining strains of *Moraxella catarrhalis* and checking whether they have the necessary cross-reactivity.

As noted on page 7 of the Office Action, it is shown in the application that the antibodies against the oligosaccharide portion of LOS of *Moraxella catarrhalis* with the specified cross-reactivity are bactericidal, opsonising and neutralizing antibodies. Additionally, the antibodies are anti-inflammatory. The effects are demonstrated in a mouse model and with human serum (Table 19). The data shows that the antibodies are functional but do not adversely affect the patient. In meningococcal disease, the finding that the medicament induces non-inflammatory, bactericidal, opsonising and neutralizing antibodies is substantive evidence that the medicament is functional. Accordingly, in contrast to the statement of the Examiner on page 7 of the Office

Action, the Applicants provided substantive evidence that the claimed composition is capable of inducing protective immunity against infection by *Neisseria meningitides*. People with ordinary skill in the art therefore can expect that the medicament confers protective immunity.

On page 7 of the Office Action, the Examiner compares the inventive antibodies to antibodies against HIV-1, which can induce neutralizing antibodies but not protection. Further, on page 9 of the Office Action, the Examiner refers to Boslego et al., showing that although a high level of serum antibody response is induced, a gonococcal pillin protein does not elicit immunity. Respectfully, the Applicants would like to point out that HIV-disease and gonococcal disease have totally different pathogenic mechanisms compared to meningococcal disease. The comparison of antibodies from HIV-disease and gonococcal disease with the antibodies from the present application is therefore not appropriate. Viral infections like HIV are chronic and intracellular. In a chronic intracellular viral infection, it is obvious that neutralizing antibodies can not provide protection to the same extent. Similarly, an antibody against a pillin protein as described by Boslego et al. is not immunogenic and can at best reduce the adherence, but not the invasion. Unlike in the present application, the antibodies of Boslego et al. do not destroy the cause of the infection.

In contrast, in meningococcal disease, the acute and major damage to the host is mediated by the inflammatory response to the LOS. Consequently, the recognition of the LOS by antibodies directly targets the LOS and the bacteria. In view of the specific mechanism of meningococcal disease, people with ordinary skill in the art would appreciate that the vaccine induces anti-inflammatory, neutralizing, bactericidal and opsonising antibodies, and therefore would understand that the antibodies are powerful vaccines, which can be used in the treatment of a meningococcal disease in passive immunisation. Indeed, the antigens are, in fact, powerful vaccines for active immunisation. Since the vaccine of the application is shown to be highly effective and not causing inflammation, the skilled person can administer it to a patient. This does not require any undue experimentation.

Presence or Absence of Working Examples

The application includes a large number of detailed working examples showing, amongst others, that the antibodies of the application are bactericidal, opsonising, neutralizing and anti-

inflammatory. The data is provided for animals and human sera. Specifically, Table 19c shows the results of experiments performed with monoclonal and polyclonal antibodies obtained from human serum absorbed with *Moraxella catarrhalis* (see also discussion on page 53, lines 17 to 32). The experiments provide substantive evidence that the vaccine of the present application is immunogenic and not harmful. Although the application does not provide a working example in which a *patient* is subjected to immunisation with the vaccine of the application, it is well-settled law that human trials are not needed to show enablement of a therapy. The working examples are highly relevant because the interactions shown are the relevant molecular interactions in the treatment of meningococcal disease.

State of the Prior Art

With respect to the elicitation of *in vivo* protective immunity, the Examiner refers to Ellis, Boslego et al. and Greenspan et al. According to the Examiner, Ellis discloses that the identification of "protein components" for preparing protective antibodies is a problem. Boslego et al., as already discussed above, relates to pillin protein antigens. Greenspan et al. states that "defining epitopes is not as easy as it seems".

As outlined above with respect to Boslego et al., publications about totally different physiological pathways must not be compared to the present medicament. In the present application it is shown that the antibodies are anti-inflammatory, bactericidal, opsonising and neutralizing, i. e., are capable of directly attacking the invasive host without negative side effects due to inflammation. The Applicants use a specific mechanism in which the antigen is selected for cross-reactivity with the meningococci and with human blood group antigens. Probably due to the homology to human blood group antigens, the antigens of the present application are not inflammatory. The pathway and the mechanism of the immune response of the present application to specific oligosaccharides are different from the immune responses to proteins as disclosed by Ellis and Boslego. Ellis and Boslego do not use an anti-inflammatory effect based on a structural homology of proteins to blood group antigens.

Furthermore, it is not understandable to the Applicants why the Examiner cites Greenspan et al. The problems outlined by Greenspan et al. with regard to defining epitopes maybe interesting on a theoretical level. In the present application, antigens were identified that

do not cause inflammation and induce bactericidal, opsonising and neutralizing antibodies. Therefore, the Applicants are of the opinion that the theoretical problems discussed by Greenspan et al. are solved by the present application. The Examiner cites from Greenspan et al.:"Accordingly, it follows the epitope to which any given antibody binds can only be identified empirically". Indeed, the Applicants have empirically determined epitopes for the production of antibodies. Greenspan et al. therefore confirms that the medicament of the present application solves a non-trivial problem and is based on an inventive step.

Quantity of Experimentation Necessary

As outlined above, the application teaches how to obtain LOS from *Moraxella catarrhalis* cross-reactive to *Neisseria meningitides* and human blood group antigens. People with ordinary skill in the art is taught that the antibodies induced according to the application are bactericidal, neutralizing, opsonising and non-inflammatory. Besides, similar but different (non-functional) vaccines were already known from Gu et al. People with ordinary skill in the art can thus obtain the medicament of the application and apply it to humans, either as the LOS antigen for active immunisation or the antibodies for passive immunisation. The application provides sufficient guidance how to use the medicament and substantive evidence that the medicament is functional. Even if one assumes that the preparation of the medicament and its application to a patient would require some experimentation from people with ordinary skill in the art, the Applicants are of the opinion that the experimentation would not be undue. It should be kept in mind that a patent application in the pharmaceutical field has no requirement to include experiments wherein the medicament is administered to a human being.

Accordingly, in view of the above arguments and amendments to the claims, withdrawal of rejections to claims 1, 2, 4, 6, 7, and 10-12 under 35 U.S.C. §112, first paragraph is requested.

II. Starting on page 10, section 5, the Examiner rejected claims 1, 2, 4, 6, 7, 10, and 11 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Similarly Applicants assume the Examiner intended to reject claims 1, 2, 4, 6, 7, and 10-12. Applicants respectfully disagree with this rejection.

Most of the arguments were already presented above with respect to the alleged lack of enablement requirement. In order to avoid redundancy, the same argument will not be presented in detail here for the written description requirement again. The Applicants will instead only present additional arguments in detail as set forth below.

The Examiner states that the claims are broadly drawn. As stated above, the claims are directed specifically to the treatment or prevention of diseases due to infection by *Neisseria meningitidis*. Because the medicament claimed in the present application is based on the pathogenic mechanism of *Neisseria meningitidis*, it is expected to be applicable to *Neisseria meningitidis* with similar pathogenic mechanisms. The claimed therapeutic indication to *Neisseria meningitidis* therefore, is directed to specific and highly related conditions so that it is believed to be drawn narrowly and not broadly. Additionally, as stated above, claim 1 is amended to claim purified LOS with cross-reactive antigens to *Neisseria meningitidis* of serogroup B and human blood group antigens. The selection of oligosaccharides of LOS with concrete cross-reactivity renders claim 1 very specific.

On top of page 12, the Examiner states: "To adequately describe the genus of LOS, applicant must adequately describe the purified lipooligosaccharides from commensal Moraxella catarrhalis that has the distinct capability to be cross-reactive with antigens to Neisseria meningitidis of the serogroup B." Respectfully, the Applicants disagree. The written description of the lipooligosaccharides from commensal *Moraxella catarrhalis* is adequate. The assays disclosed for checking cross-reactivity of LOS oligosaccharides to antigens of *Neisseria meningitidis* and human blood group antigens are repeatable methods for determining if the lipooligosaccharides from *Moraxella catarrhalis* are useful according to the application and claim 1. Since cross-reactivity is the essential feature of the required LOS, the definition of the LOS by cross-reactivity is adequate. In this respect, it is not relevant that Greenspan et al. "recommend defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody" (as noted by the Examiner on page 12, 3rd paragraph). The subject of Greenspan et al. is a scientific study about the characterization of antigen/antibody interactions. In contrast, a present application is a practical guidance to people with ordinary skill in the art to make use of an invention. In a patent application, the relevant

question is whether the invention is sufficiently enabled and repeatable, and not that the structure of a component is perfectly understood on a theoretical level.

With regard to the Examiner arguments about the relation of species to a genus from page 13 to page 14, the Applicants respectfully submit that the application has described distinguishing identifying characteristics to show that the Applicants were in possession of the claimed invention. Specifically, the Applicants identified that LOS from *Moraxella* catarrhalis has cross-reactive antigens to Neisseria meningitides and human blood group antigens. The LOS induces non-inflammatory, bactericidal, opsonising and neutralizing antibodies that are functional. The scope of the claims is not overly broad, because the definition of the LOS is very specific. Accordingly, withdrawal of this rejection is requested.

35 USC § 102

Examiner rejected claims 1, 4, 6, 7, 10, and 11 under 35 U.S.C. §102 as being anticipated by Gu et al. (U. S. Patent No. 6,685,949). Applicants understand that the Examiner intended to make out a rejection of claims 1, 4, 6, 7, and 10-12. Claim 1 has been amended to include limitation from the original Claim 2, which is not rejected by the Examiner. In view of the amendment, the rejection is obviated.

The Examiner notes that Gu et al. disclose vaccines comprising lipooligosaccharides from *Moraxella catarrhalis,* from which either the esterified fatty acids or the Lipid A portion are removed (column 3, lines 42 to 48). Therefore, in the first embodiment when only the fatty acids are removed, the vaccine allegedly would be a vaccine according to claim 1. With all due respect, the assumption that such vaccines are identical to the vaccines of the present application as defined by claim 1 is not correct. The present application as defined by claim 1 requires that LOS from *Moraxella catarrhalis* or antibodies against such LOS is used as a vaccine. The present application further requires a specific selection of *Moraxella catarrhalis* LOS. At first, the oligosaccharides of the LOS must be cross-reactive antigens to *Neisseria meningitidis* of the serogroup B. Secondly, the oligosaccharides of the LOS must be cross-reactive with human blood group antigens. The cross-reactivity of meningococcal LOS with human blood group antigens is a basic element of meningococcal disease. The meningococcal strains carrying these

antigens mimic human blood group antigens and resist complement-mediated killing (see page 8, lines 9 to 26 and page 9, line 22 to page 10, line 13 of the specification.)

The LOS of *Moraxella catarrhalis* and *Neisseria meningitides* neither share a common core structure nor the same Lipid A moieties. This is outlined in the description from page 14, line 1 to line 25. There is some limited similarity with respect to the 2 KDO molecules of the inner core attached to Lipid A. However, these molecules do not show a homology to human blood group antigens. In contrast, the Applicants found that there is a homology between the oligosaccharide portion (α-chain or variable LOS region 1, see page 6, line 26 to page 7, line 28 of the application) of *Moraxella catarrhalis*, the oligosaccharide portion of *Neisseria meningitidis* and the human blood group antigens. This is summarized on page 17, lines 29 to 32 of the present application:

> "Although LOS from Moraxella catarrhalis differs structurally from meningococcal LOS, both species share some homology in their oligosaccharide chain moieties. Terminal oligosaccharide residues found on the non-reducing end of Moraxella catarrhalis LOS share some homology with human blood group antigens".

Gu et al. do not teach or suggest a selection for cross-reactivity. In fact, the majority of *Moraxella catarrhalis* strains do not have LOS that is cross-reactive with *Neisseria meningitidis* antigens as well as human blood group antigens. Consequently, a vaccine of Gu et al. lacking this cross-reactivity is ineffective as a vaccine against *Neisseria meningitidis.*

Gu et al. use a *Moraxella catarrhalis* LOS preparation as a vaccine against *Moraxella catarrhalis.* They use a *Moraxella catarrhalis* strain 25238, which is of serogroup A (see column 15, line 26, column 17, line 24, column 23, line 71). In meningococcal disease, serogroup A strains of *Moraxella catarrhalis* are not cross-reactive with *Neisseria meningitidis* LOS as well as human blood group antigens, because they lack the cross-reactive oligosaccharides. As a support, the Applicants respectfully submit an article published by Braun et al. (vaccine 22 (2004), pages 898-908). This publication is a study about the cross-reactive antigens shared by *Neisseria meningitidis, Moraxella catarrhalis* and human blood. In Table 3 on page 901, Braun et al. summarized which LOS types of *Moraxella catarrhalis* are homologues to which human blood group antigens and meningococcal immunotypes. Only the

LOS types of *Moraxella catarrhalis* are relevant because they are homologues to meningococcal immunotypes that cause meningococcal disease. In the application it is outlined that the meningococcal immunotypes related to disease are L(3,7,9) (page 8, lines 8 to 26 and page 16, lines 16 to 25). The immunotypes are found in group B and C outbreak strains.

Table 3 of Braun et al. shows that only some immunotypes of *Moraxella catarrhalis* of group C, namely C8 and C10, show cross-reactivity with the meningococcal invasive immunotypes L(3,7,9). The LOS of type A are not homologous to invasive meningococcal strains of serogroup B. The vaccines disclosed by Gu et al. thus do not fulfil the cross-reactivity requirements of claim 1 and are not useful in the treatment or prevention of meningococcal disease.

Type A is the major antigenic type of LOS in *Moraxella catarrhalis*. As outlined in Gu et al., column 2, lines 56 to 59, the major antigenic types A, B and C of LOS account for 95 % of *Moraxella catarrhalis* strains, from which 61 % are type A, 29 % type B and 5 % type C. From type C only certain subtypes show homology with meningococcal L(3,7,9). Therefore, without selecting *Moraxella catarrhalis* LOS with cross-reactivity to *Neisseria meningitidis* of serogroup B and human blood group antigens it is unlikely to select by chance a strain from *Moraxella catarrhalis* which fulfils the requirements of claim 1. Accordingly, withdrawal of this rejection is requested.

CONCLUSIONS

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

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